

A New Era of CUP Diagnosis and Therapy: Why is There Controversy and Lack of Global Acceptance?

- When is there enough evidence to change the approach in CUP?
- Are randomized prospective phase III trials always necessary to change the approach?
- Is substantial aggregate data and/or very strong circumstantial evidence persuasive?
- “promoting action that leads to improved diagnosis & the end of CUP” is in process.

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- Treatment of many patients with various advanced cancers is improving rather rapidly with sequential therapies including targeted drugs and immune stimulating drugs
- New era of CUP diagnosis. About 95% of CUP have their cancer type diagnosed from a biopsy of a metastatic site by IHC and/or a molecular cancer classifier assay. To improve accuracy and confidence in these diagnoses, the clinical features and morphology of the biopsy are always important to consider in concert with the IHC and molecular findings.
- The diagnosis of the cancer type is correct for most patients.

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- A large, prospective study and several retrospective studies show outcomes for many CUP patients are improved by site-specific therapy based on diagnosis of their cancer type
 - Prospective trial – median survivals of molecularly diagnosed CUP patients similar to their counterparts with known types of advanced cancers
 - More responsive cancer types diagnosed by molecular assay or IHC have much longer survival than less responsive cancer types.
- Retrospective studies – Survival of CUP patients diagnosed with colorectal or renal cancer by IHC and/or molecular diagnosis is similar to survival of their counterparts with known advanced colorectal and renal carcinomas

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- If chemotherapy is considered in CUP, does one choose an empiric regimen (broad-side or shotgun therapy) or site-specific therapy based on their cancer type?
- There are hazards to the patient in not adopting the new paradigm. Consider risk versus benefit. Many cancer types now have better therapy. Cost is a concern but savings possible (i.e. PET rarely needed).

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- Confirmatory data will be necessary for some to change their mind and approach to treatment of CUP patients
 - Randomized prospective trials – European study
 - Difficult with heterogeneity of CUP
 - Will need to randomly compare specific groups (i.e. colorectal), empiric versus site-specific therapy

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- Optimal management of CUP – 2015
 - Standard evaluation looking for anatomical primary site
 - Biopsy of metastatic site – tissue management
 - Pathologic review and IHC
 - Save small amount of block (2 unstained slides) for molecular study if necessary

Continued

- If IHC diagnostic of single cancer type the evaluation is finished if clinical features / morphology of the biopsy is consistent.
- If IHC not diagnostic of a single cancer type a molecular cancer classifier assay should be obtained.
- If single cancer type diagnosed by IHC and/or molecular assay, treat the patient for this cancer type.
- For selected cancer types (lung, breast, melanoma, gastric/GE junction, colorectal, others) obtain additional genetic studies on the biopsy looking for known actionable alterations.

Changing Landscape for CUP

	CUP in 1976	CUP in 2015
<u>Clinical Evaluation</u>	Rudimentary CT not yet available	Can be extensive CTs, PET, MRI, endoscopies
<u>Pathology</u>	H&E; no helpful IHC stains	Evolving IHC useful, Molecular diagnosis useful; cancer type defined in 95%
<u>Treatment</u>	Symptomatic/supportive No effective Rx No specific diagnoses Empiric regimens	Most often site-specific directed at likely primary site
<u>Favorable subset</u>	NOT appreciated; just started to recognize	Multiple subsets now appreciated with specific treatments
<u>Prognosis</u>	Very poor; all patients lumped together; only a few known solid tumors had useful therapy	Good for favorable subsets Better with site-specific therapy based upon an accurate diagnosis of the primary site/cancer type. Poor for specific tumors with ineffective therapy